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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
KIM, TAEYOON

ART UNIT	PAPER NUMBER
1651	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/823,647	THIRUVENGADAM ET AL.	
	Examiner	Art Unit	
	Taeyoon Kim	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34,38,44-46 and 48-51* is/are pending in the application.

4a) Of the above claim(s) *1-26,33,34,38,44,46 and 48-51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-32 and 45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

It is not understood up to now why there are discrepancies between studies based on the activity of Na^+K^+ ATPase. The current application does not explain the deficiency of such method for diagnosis of bipolar disorder. The measurement of transmembrane potential in various groups of patients and/or control would be enabling. However, it is not only the question of whether the method step is enabling, but whether the intended use of diagnosing bipolar disorder based on the sodium pump activity. The instant application did not establish such critical question in the art. Without knowing why there have been contradicting and controversial results from different studies, transmembrane potential would be still under question whether it is a reliable basis to diagnose bipolar disorder no matter what kind of modification to the methods made. The parameters associated with the activities of sodium pump would be the secondary to the main issue of such measurement on the activity of sodium pump, and would not guarantee for the use of such method in diagnosis of bipolar disorder. Furthermore, as El-Mallakh et al. and Buss et al. disclosed, transmembrane potential measured by the same method of the current invention showed no difference between bipolar patients and normal control. Since the method of measuring transmembrane potential of El-Mallakh et al. and Buss et al. is considered identical as the one disclosed in the current invention, a person of ordinary skill in the art would have expected the same result obtainable from the method of the instant invention.

Applicant discussed methods in the response such as "Ratio Method." The examiner respectfully points out that such method is not an applicant's invention and it is well known in the art that such method is used to calculate the relationship between

DETAILED ACTION

Claims 1-34, 38, 44-46 and 48-51 are pending.

Response to Amendment

Applicant's amendment and response filed on Mar. 2, 2007 has been received and entered into the case.

Claims 1-34, 38, 44-46 and 48-51 are pending, claims 1-26, 33, 34, 38, 44, 46, 48-51 are withdrawn from consideration as being drawn to non-elected subject matter. Claims 27-32 and 45 have been considered on the merits. All arguments have been fully considered.

The claim rejections under 35 U.S.C. §112, 2nd paragraph based on the terms "cells" and "a patient" are withdrawn due to the amendment.

The claim rejection under 35 U.S.C. §112, 2nd paragraph based on the term "significantly" and "significant" in claim 27 is withdrawn because of definition of "significant difference" given in the specification as $p<0.05$ (see p.40, line 22 of the specification).

Applicant's arguments with respect to rejection under 35 U.S.C. §112, 2nd paragraph based on the phrase "... one or more people..." have been fully considered and are persuasive. The rejection of claims 27-32 and 45 has been withdrawn.

The rejection on claim 30 based on 35 U.S.C.§112, 1st written description has been withdrawn.

The rejection to claims 27-32 and 45 based on 35 U.S.C.§112, 1st scope of enablement and written description has been withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27-32 and 45 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The method of the current claims is based on the assumption that there is a significant difference in membrane potential mediated by sodium pump (Na^+K^+ ATPase) between bipolar patients and normal control. However, it is controversial whether the activity of sodium pump for diagnosing bipolar disorder can be used as a reliable basis, evidenced by contradicting results from El-Mallakh et al. (1996) and Buss et al. (1996). Even further, applicant stated in the specification (p. 7, lines 1-9) "one would not expect Na^+K^+ ATPase activity to serve as a reliable basis for diagnosing bipolar disorder in an individual patient, because measurements of Na^+K^+ ATPase activity are highly variable", and applicant has further disclosed that it is not reliable to use transmembrane potential to serve as a basis of diagnosing bipolar disorder. It is contradicting statement because applicant also disclosed in the specification (p. 8, lines 9-13) that they found the membrane potential in cultured cells from bipolar patients is significantly different than the membrane potential in cultured cells from unaffected controls and siblings.

Therefore, based on these contradicting evidences from applicant's own disclosures and the prior art references, the method of the current claims would not have a reasonable expectation of success for a person of ordinary skill in the art at the time of invention made to use for diagnosis of bipolar disorder.

In the response filed on Mar. 2, 2007 to the office action mailed on Nov. 3, 2006, applicant argued that 1) the examiner has not indicated where in the specification applicant state that "it is not reliable to use transmembrane potential to serve as a basis of diagnosing bipolar disorder," 2) even if the statement were made by the applicant, it only makes an observation concerning the difference in membrane potential between two groups of cells, and 3) a reproducible and reliable assay has been accomplished in the instant application.

First of all, the examiner did not argue that the exact statement quoted is in the specification. Rather, the specification says, "Similarly, one would not expect transmembrane potential to serve as a reliable basis for diagnosing a bipolar disorder in an individual patient, because measurements of transmembrane potential are highly variable." (see p.7, lines 7-11)

Applicant argued that the method of El-Mallakh et al. and Buss et al. generated contradicting data because the measurement of the references being fraught with the errors in measurement. This argument is merely the argument of counsel and is unsupported by evidence or declarations of those skilled in the art. Attorney argument is not evidence unless it is an admission, in which case, an examiner may use the admission in making a rejection. See M.P.E.P. § 2129 and § 2144.03 for a discussion of

admissions as prior art. Counsel's arguments cannot take the place of objective evidence. *In re Schulze*, 145 USPQ 716 (CCPA 1965); *In re Cole*, 140 USPQ 230 (CCPA 1964); and especially *In re Langer*, 183 USPQ 288 (CCPA 1974). See M.P.E.P. § 716.01(c) for examples of attorney statements that are not evidence and that must be supported by an appropriate affidavit or declaration.

It is not understood up to now why there are discrepancies between studies based on the activity of Na^+K^+ ATPase. The current application does not explain the deficiency of such method for diagnosis of bipolar disorder. The measurement of transmembrane potential in various groups of patients and/or control would be enabling. However, it is not only the question of whether the method step is enabling, but whether the intended use of diagnosing bipolar disorder based on the sodium pump activity is enabling. The instant application did not answer such critical question. Without knowing why there have been contradicting and controversial results from different studies, transmembrane potential would be still under question whether it is a reliable basis to diagnose bipolar disorder no matter what kind of modification made to the methods. The parameters associated with the activities of sodium pump would be the secondary to the fundamental question of whether measuring and comparing transmembrane potential provides reliable basis for diagnosing bipolar disorder. As Buss et al. disclosed, transmembrane potential measured by the same method of the current invention showed no difference between bipolar patients and normal control. Since the method of measuring transmembrane potential of Buss et al. is considered identical as the one

disclosed in the current invention, a person of ordinary skill in the art would have expected the same outcome from the method of the instant invention.

Applicant argues that the references cited are old and the method used at that time might not be reliable, and applicant has overcome such obstacle in the current invention so that the method can serve as a reliable basis for diagnosing bipolar disorder.

The question to ask is whether the controversial results from various "old" studies were due to the technical problems that might be present at that time, or there is a fundamental problem in the use of transmembrane potential in diagnosing bipolar disorder. Applicant asserted that it is presumably due to the technical problems. Although applicant discloses various parameters considered in the method of diagnosing bipolar disorder, the method per se is the same as those taught by the references. The method in the references utilizes the same fluorescence dye loaded in the presence or absence of ligands, which activate sodium pump, and the fluorescence intensity was measured using a fluorescence spectrometry. And the method also obtains the ratio between groups to compare. The method steps and apparatus used in the method taught by the references are considered the same. There is no technical advancement provided by the current invention. Applicant discussed methods in the response such as "Ratio Method." The examiner respectfully points out that such method is not an applicant's invention and it is well known in the art that such method is used to calculate the relationship between fluorescence intensity used in the measurement of membrane potential and El-Mallakh et al. as well as Buss et al. utilized

the same ratiometric measurement using fluorescence dye. Therefore, it is the examiner's position that the discrepancy from the prior art in using the transmembrane potential in diagnosing bipolar disorder is due to the unreliable nature of sodium pump activity measured by transmembrane potential.

Unless applicant provides evidence that the discrepancies in the prior arts are merely due to the technical problems rather than fundamental problem of reliable basis for diagnosing bipolar disorder, the examiner takes the position that the current invention would not enabling for the intended use of "diagnosing a bipolar disorder."

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 27-32 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over El-Mallakh et al. (1996) in light of Garrahan et al. (1967) or Antia et al. (1995).

Claims 27-32 and 45 are drawn to a method for diagnosing a bipolar disorder by comparing ratios of the mean membrane potential in the presence and absence of a compound altering sodium pump of a patient with the ratios from both positive and negative control, and under the condition of the presence or absence of potassium. The claims also disclose a variety of different compounds altering the activity of sodium pump including ethacrynate.

El-Mallakh et al. teach a method of measuring transmembrane potential (TMP) from leukoblasts isolated from bipolar patient and control in the absence or presence of gramicidin, the relative TMP, calculated from the ratio of TMP in the absence and TMP in the presence of gramicidin (depolarizing agent), and then compares the difference to distinguish the patient and the control (whole document; especially see p.199, 2.3. TMP measurement).

Although El-Mallakh et al. do not particularly teach the use of various combination of presence or absence of potassium during the measurement, it would have been obvious for a person of ordinary skill in the art to utilize various different conditions including in the presence or absence of potassium ion (see Garrahan et al.). This is because the ratio of TMP obtained in the absence of potassium would provide better understanding of the activity of sodium pump, and would provide additional data for the comparison between a patient and controls. Thus, a person of ordinary skill in the art recognizes the condition of the absence of potassium as a parameter to optimize

the outcome of the method of El-Mallakh et al. to distinguish the difference between a bipolar patient and control.

The US Federal Circuit has recently explicitly stated that in order to make a *prima facie* case of obviousness, the suggestion and motivation to combine said references need not be explicitly stated in the text of the references. Rather, consideration of common knowledge and common sense when combining references is not only permitted *but required*. See DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co., 80 USPQ2d 1641 (Fed. Cir. 2006) which states:

> ""Suggestion" test for obviousness does not require that suggestion, teaching, or motivation to combine cited prior art references be found in references themselves, or that such suggestion or motivation be explicitly stated; suggestion test is flexible rather than rigid and categorical, recognizing motivation to combine found in knowledge of persons of ordinary skill in art or nature of problem to be solved, as well as in references, and test not only permits, but requires, consideration of common knowledge and common sense."

Although El-Mallakh et al. do not teach the use of ethacrynate, it is well known in the art that ethacrynate is a compound to activate sodium pump as supported by Antia et al., and therefore considered as an art-recognized equivalent to gramicidin used in the method of El-Mallakh et al. M.P.E.P. §2144.07 states "The selection of a known material based on its suitability for its intended use supported a prima facie obviousness determination in Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945) (Claims to a printing ink comprising a solvent having the vapor pressure characteristics of butyl carbitol so that the ink would not dry at room temperature but would dry quickly upon heating were held invalid over a reference teaching a printing ink made with a different solvent that was nonvolatile at room temperature but highly

volatile when heated in view of an article which taught the desired boiling point and vapor pressure characteristics of a solvent for printing inks and a catalog teaching the boiling point and vapor pressure characteristics of butyl carbitol. "Reading a list and selecting a known compound to meet known requirements is no more ingenious than selecting the last piece to put in the last opening in a jig-saw puzzle." 325 U.S. at 335, 65 USPQ at 301.)".

Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill at the time the invention was made.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Taeyoon Kim whose telephone number is 571-272-9041. The examiner can normally be reached on 8:00 am - 4:30 pm ET (Mon-Fri).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic

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